

Bugs vs Drugs:

Charting a Course for Our Profession



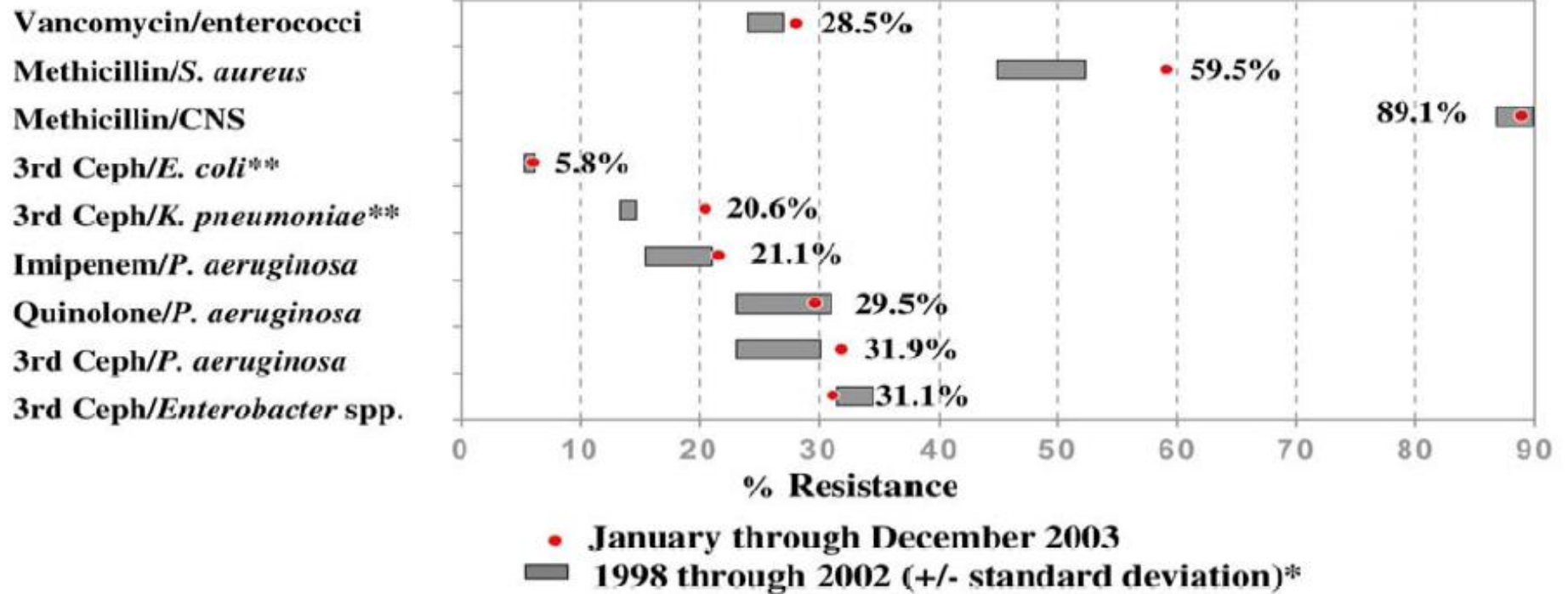
Christopher A. Ohl MD

Director, Center for Antibiotic
Utilization, Stewardship and
Epidemiology

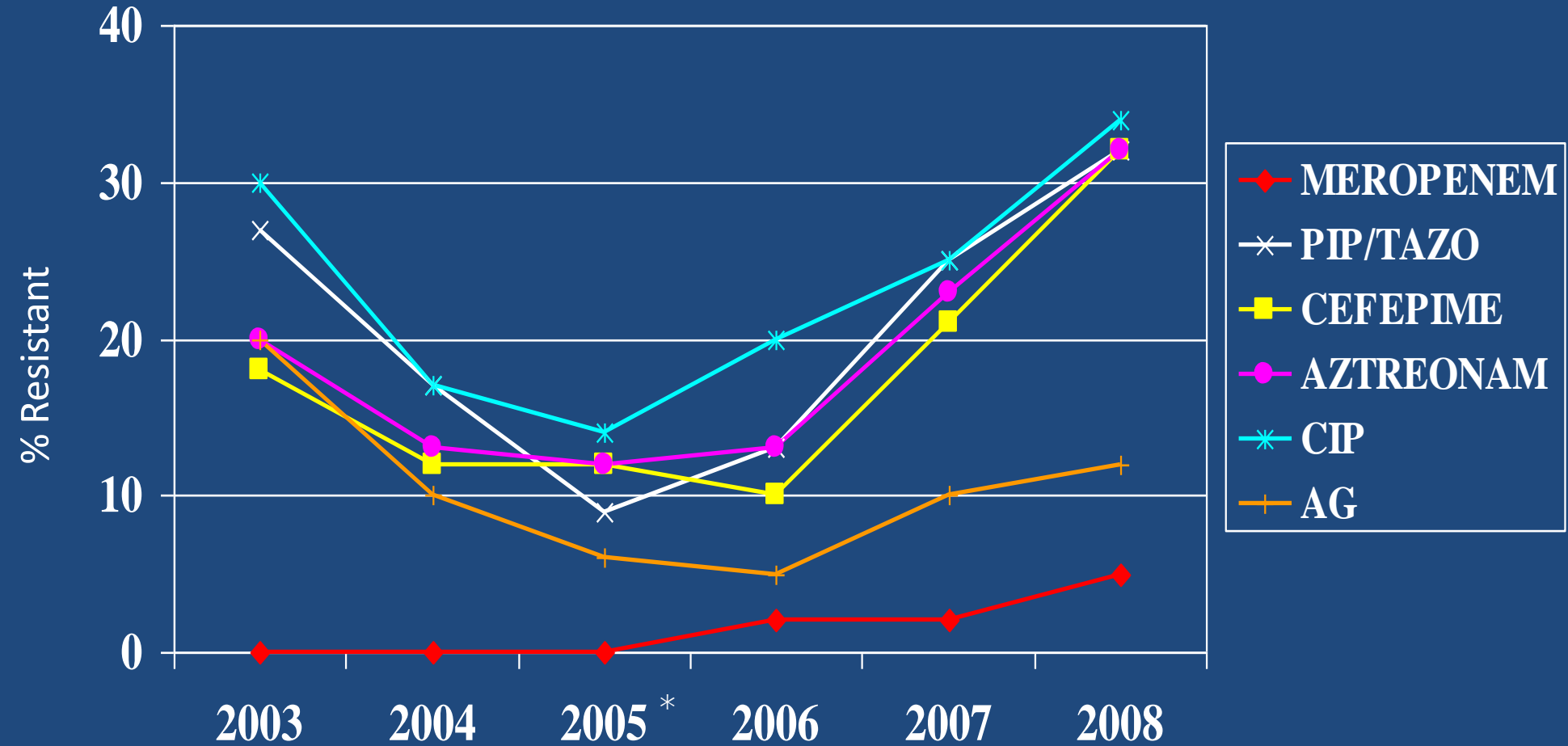
Associate Professor of Medicine

Wake Forest
School of Medicine

NNIS Data - 2003

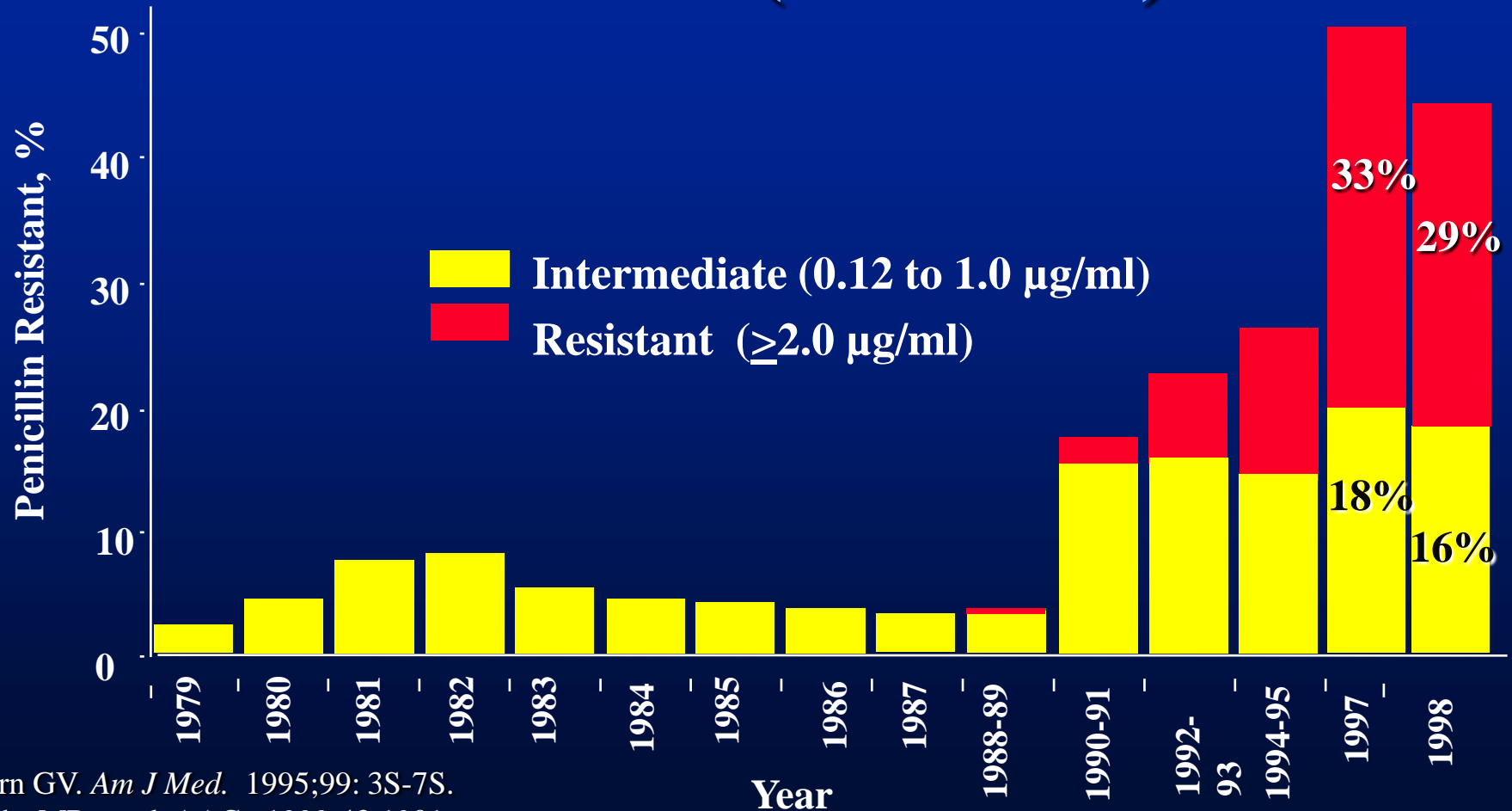


K. pneumoniae (ICU) WFUBMC



Penicillin-Resistant *S. pneumoniae*

United States (1979-1997)



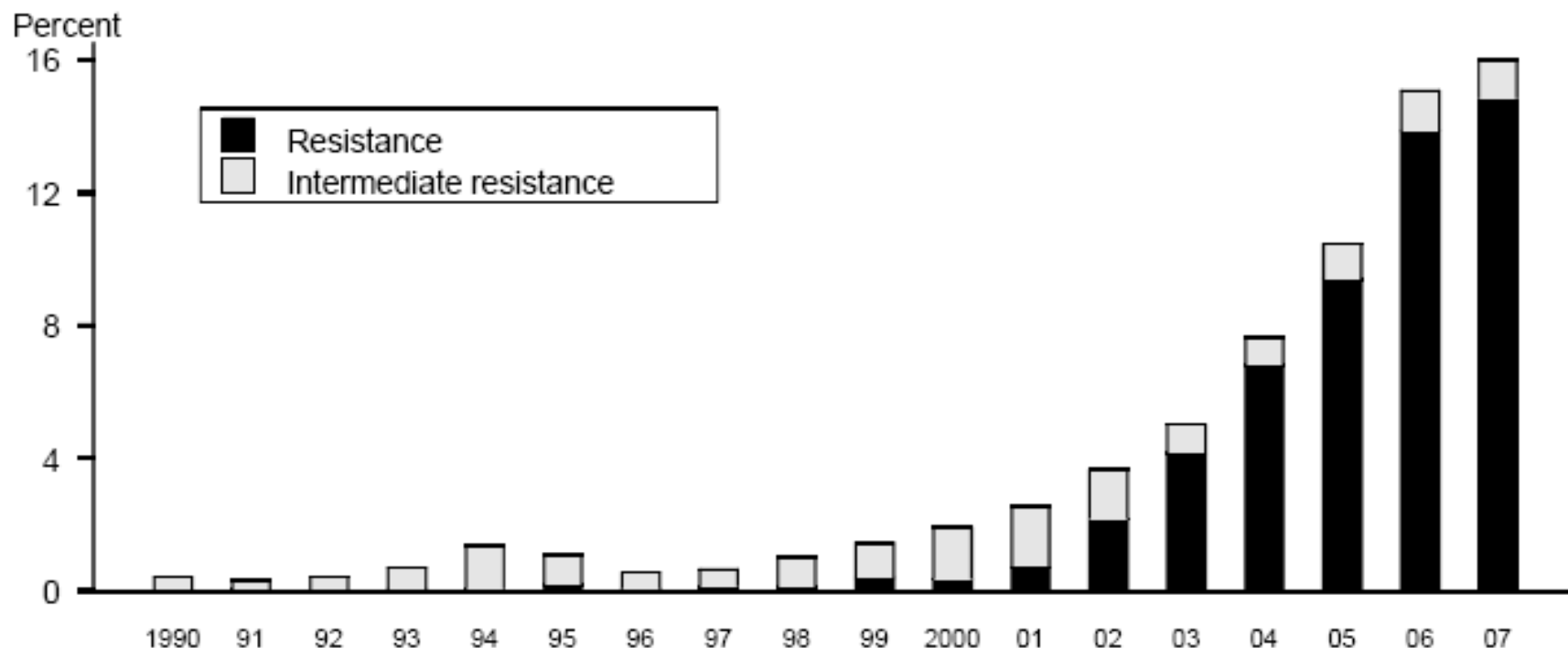
Doern GV. *Am J Med.* 1995;99: 3S-7S.

Jacobs MR, et al. *AAC.* 1999;43:1901.

Jacobs MR, et al. *ICAAC.* 1999; Abstract C-61.

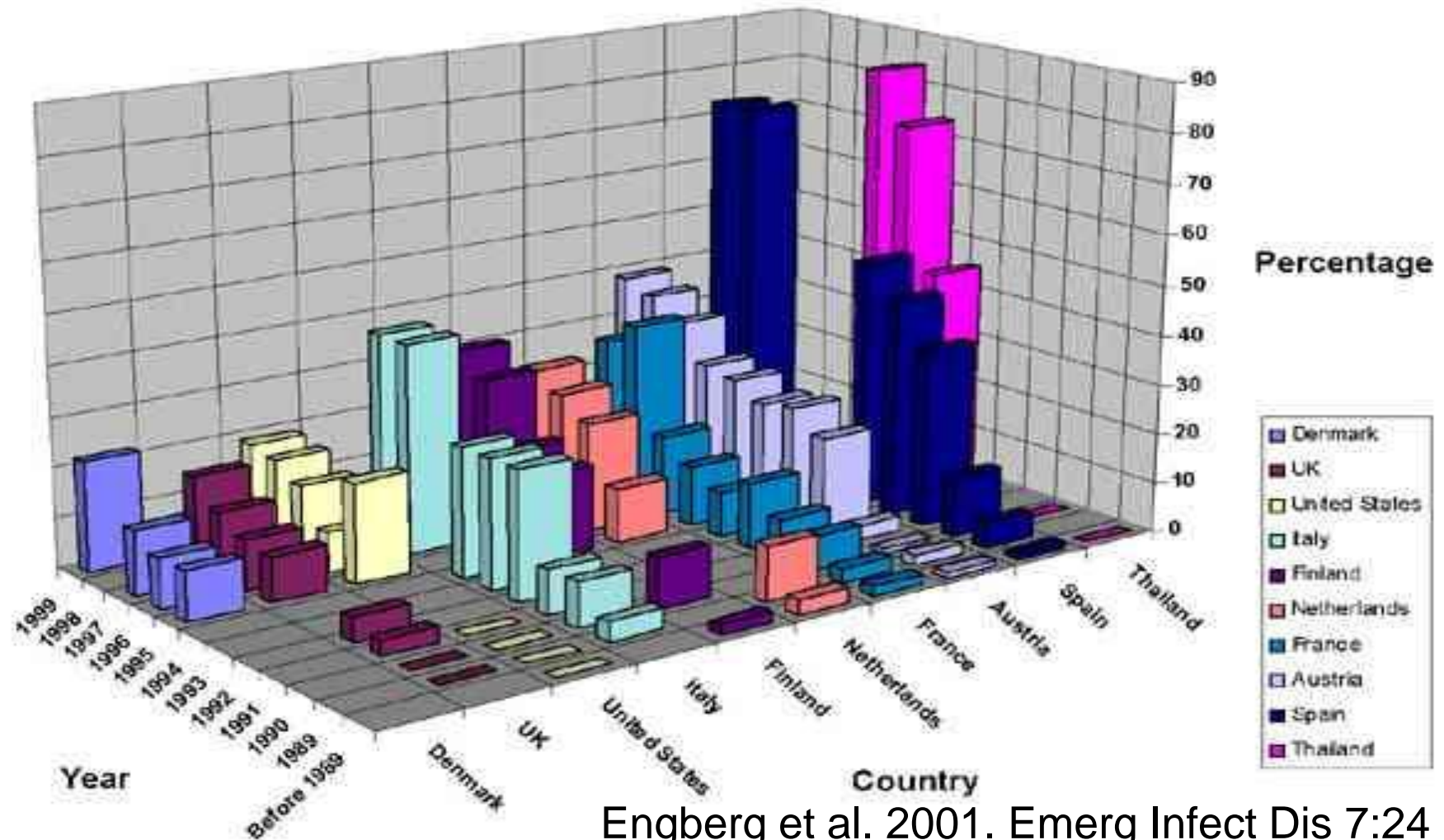
Fluoroquinolone resistant gonorrhea

Figure 16. Percentage of GISP isolates with intermediate resistance or resistance to ciprofloxacin, 1990-2007



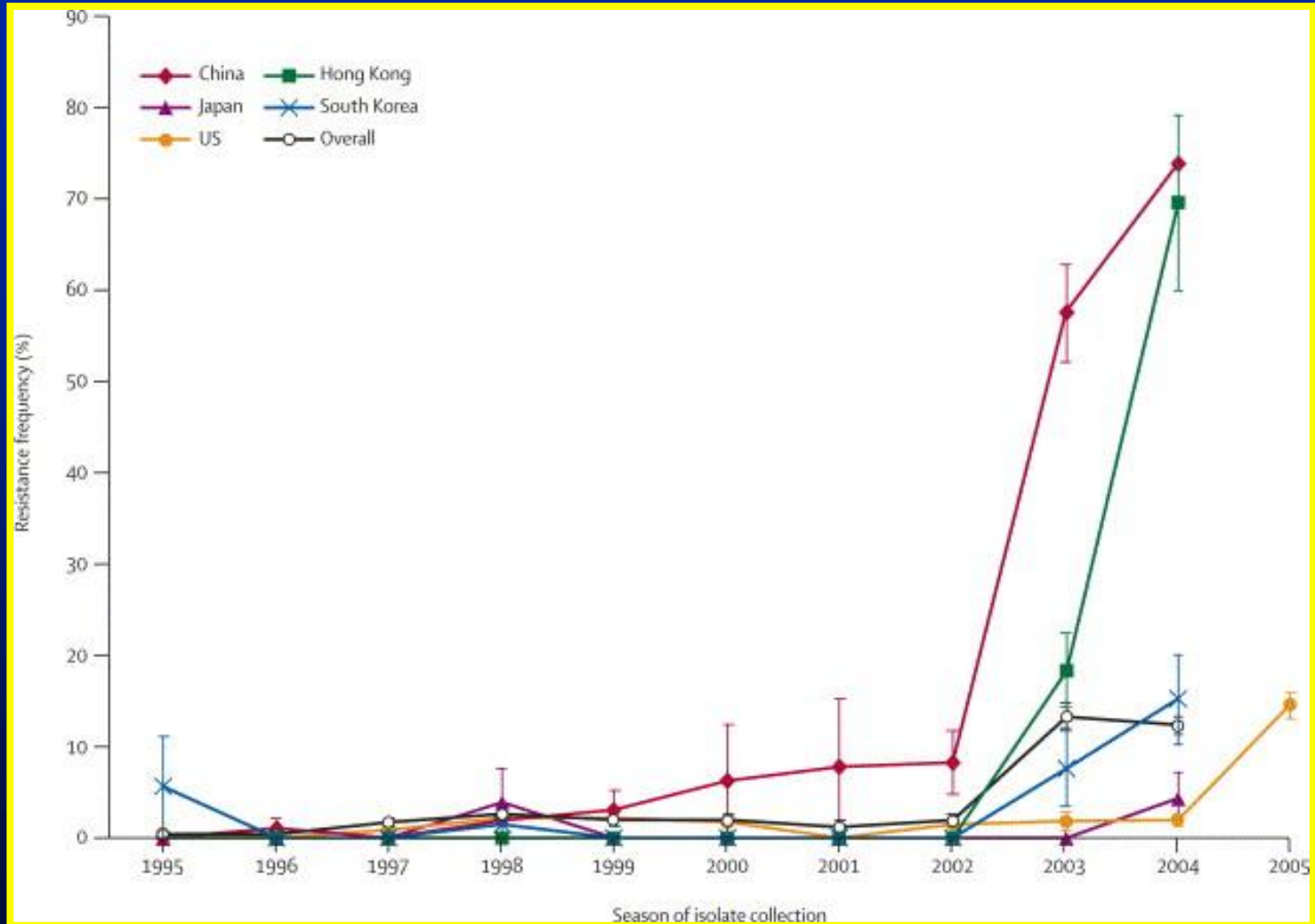
Campylobacter jejuni & *C. coli*

Quinolone Resistance



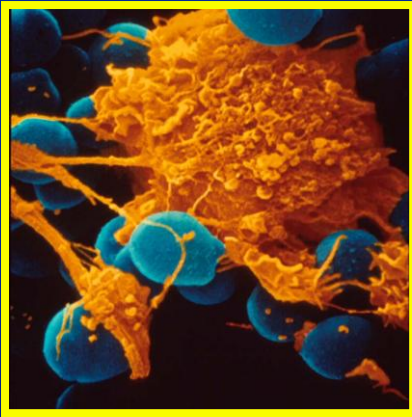
Engberg et al. 2001. Emerg Infect Dis 7:24

Amantadine Resistance in Influenza



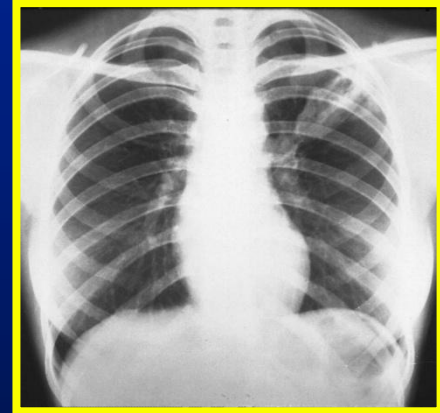
Bright et al. Lancet 2005. 366:1175

Not Just Bacteria



Candida sp. resistant to Imidazoles

Multiple Drug Resistant Tuberculosis

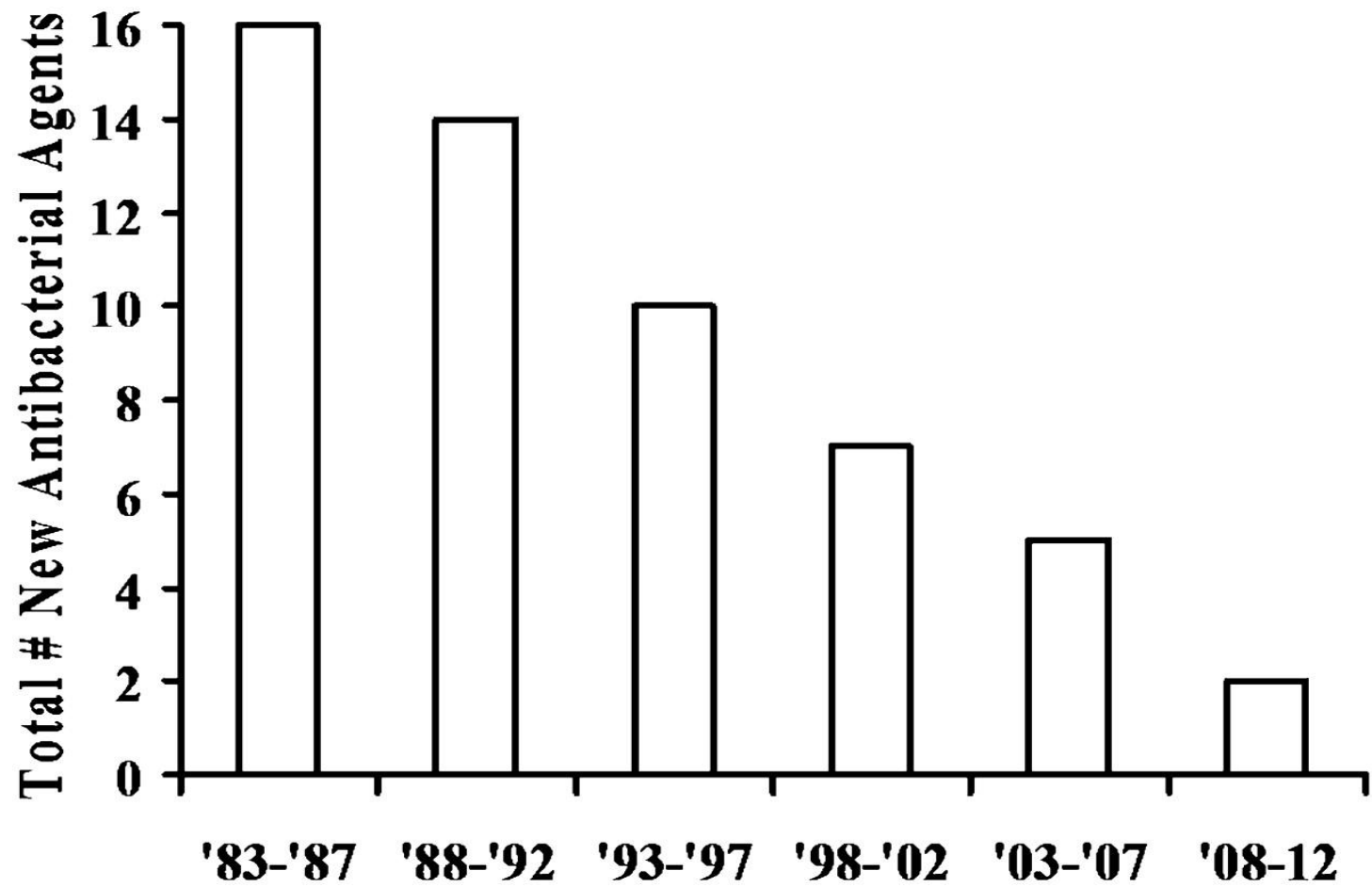


Multiple Drug Resistant Malaria

ORGANISM >100,000 CFU/ML ACINETOBACTER SPECIES

<u>SENSITIVITY</u>	<u>MSCAN MIC</u>	
AMIKACIN	>32	RESISTANT
AMPICILLIN/SULBACTAM	>16/8	RESISTANT
CEFEPIME	>16	RESISTANT
CEFTAZIDIME	>16	RESISTANT
CIPROFLOXACIN	>2	RESISTANT
GENTAMICIN	>8	RESISTANT
MEROPENEM	>8	RESISTANT
PIPERACILLIN	>64	RESISTANT
TETRACYCLINE	>8	RESISTANT
TOBRAMYCIN	>8	RESISTANT
TMP/SMX	>2/38	RESISTANT
POLYMYXIN B	8	RESISTANT

Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.



Clin Infect Dis. 2011;52:S397-S428

The Pipeline

**Promising new drugs for resistant
gram-negatives**

THE WALL STREET JOURNAL.

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U.S. EDITION Tuesday, November 10, 2009

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Adelson to Keep
Betting on the GOP

3 of 12



HEALTH INDUSTRY | November 10, 2009

Pfizer Shuts Six R&D Sites After Takeover

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By JONATHAN D. ROCKOFF

Pfizer Inc., PFE +1.89% digesting its \$68 billion takeover of rival Wyeth last month, said Monday it will close six of its 20 research sites, in the latest round of cost cutting by retrenching drug makers.

Pfizer was expected to cut costs as part of its consolidation with Wyeth, and research and development was considered a prime target because the two companies' combined R&D budgets totaled \$11 billion. In announcing the laboratory shutdowns Monday, Pfizer didn't say how many R&D jobs it would cut or how much it hoped to save from the shutdowns.



IDSA May 2011 Policy Paper

www.idsociety.org

- Create statutorily defined incentives for antibiotic research and development .
- Support R&D of new rapid diagnostic tests.
- Recalibrate unworkable FDA requirements for new antibiotic approvals.
- Strengthen federal coordination, accountability, and transparency by designating an office/director within the HHS to lead the existing federal Interagency Task Force on Antimicrobial Resistance.
- Aggressively promote the judicious use of currently available antibiotics through the adoption of antimicrobial stewardship programs as well as better infection control practices.

A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

Interagency Task Force on Antimicrobial Resistance

- 2011 Federal Action Plan that coordinates Federal Response to AR (Updated 2012)
- Surveillance
- Prevention and Control
- Research
- Product Development
- Advocates establishing an office in HHS to implement and have ownership of the plan

STARR Act

- Comprehensive Bill that would enact much of the recommendations of ITFAR
- Introduced in House in 2009
- No action to date



Antibiotic Use Leads to Antibiotic Resistance



Outpatient

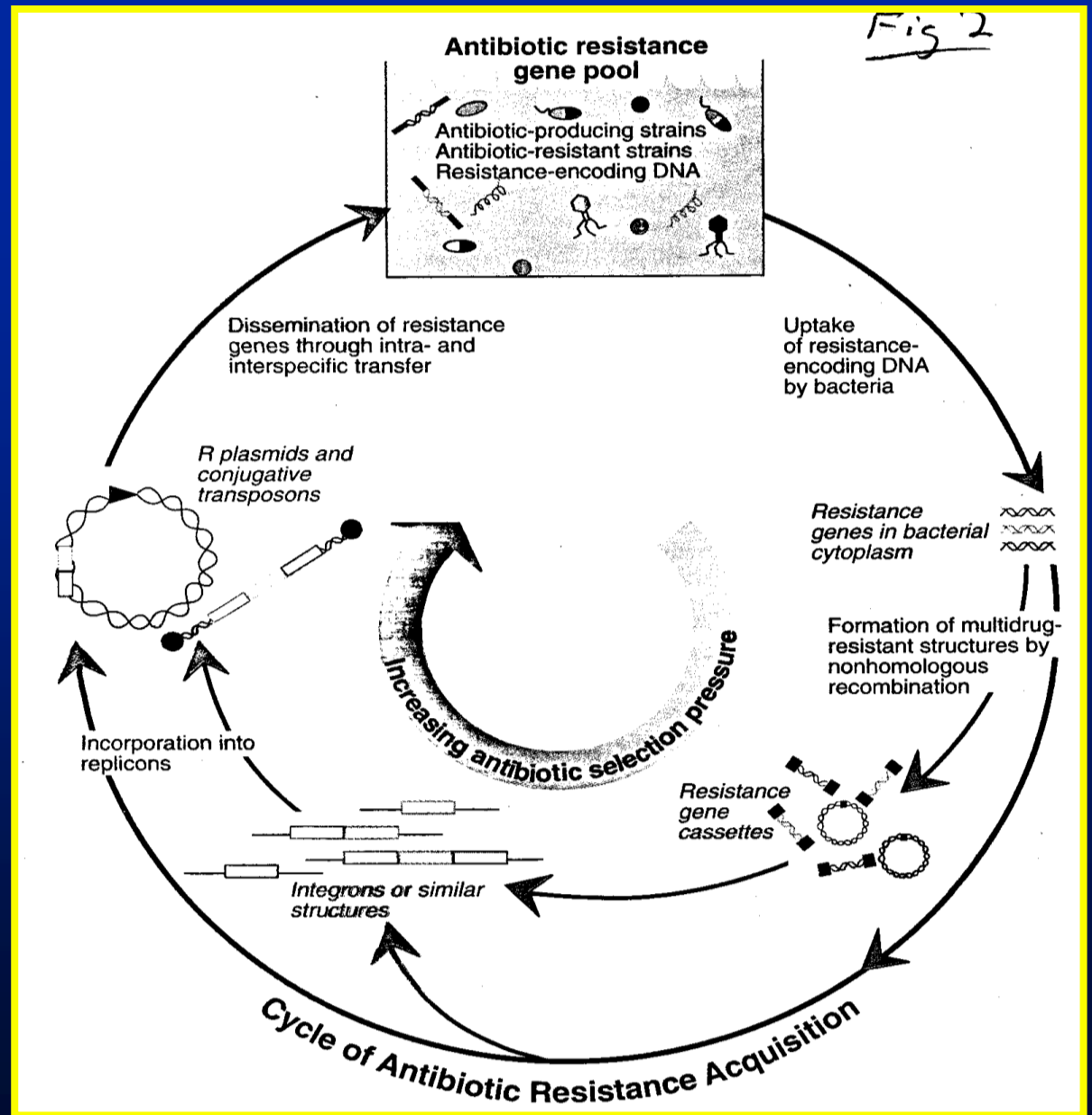
Inpatient



Agriculture

Cycle of Antibiotic Resistance Acquisition

Under
Increasing
Antibiotic
Selection
Pressure



Consequences of Hospital Antibiotic Use

- At one tertiary care center 70% of Medicare patients received an antibiotic in 2010
- Approximately 50% of this use was unnecessary or inappropriate
- Untoward consequences of antibiotic therapy identified in this and other studies:
 - Inadequate treatment of infection
 - Increased hospital readmissions
 - ADEs



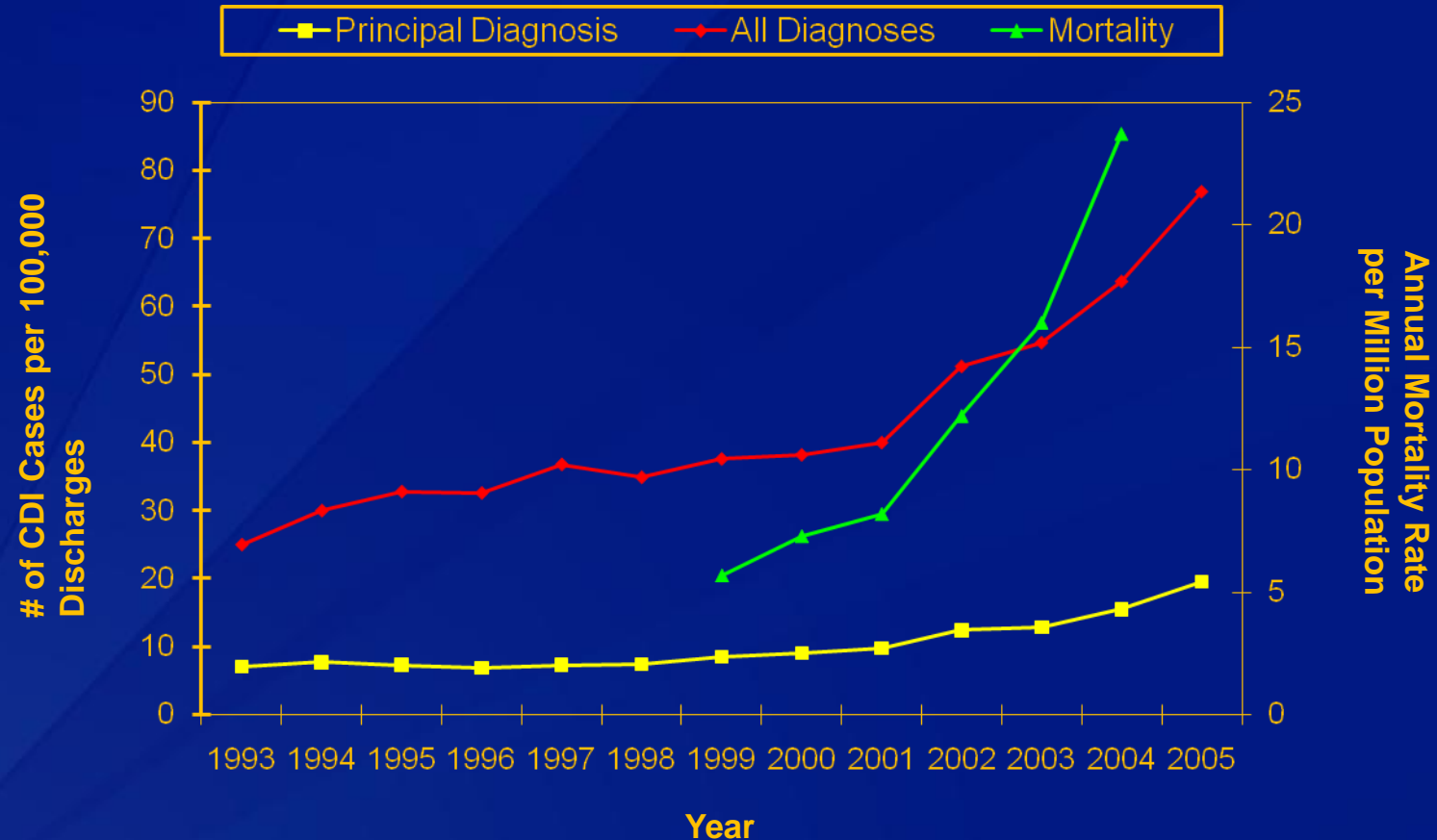
Inappropriate Antimicrobial Management at the Level of the Patient

- Good intentions
- Inappropriate dosing
- Inappropriate prophylaxis
- Continuation of multiple or broad-spectrum agents
- Pressure from the patient
- Time constraints



Ohl CA, Luther VP. J Hosp Med 2011
Polk et al. In: PPID, 6th ed. 2005

Incidence and mortality of *Clostridium difficile* infections are increasing in US

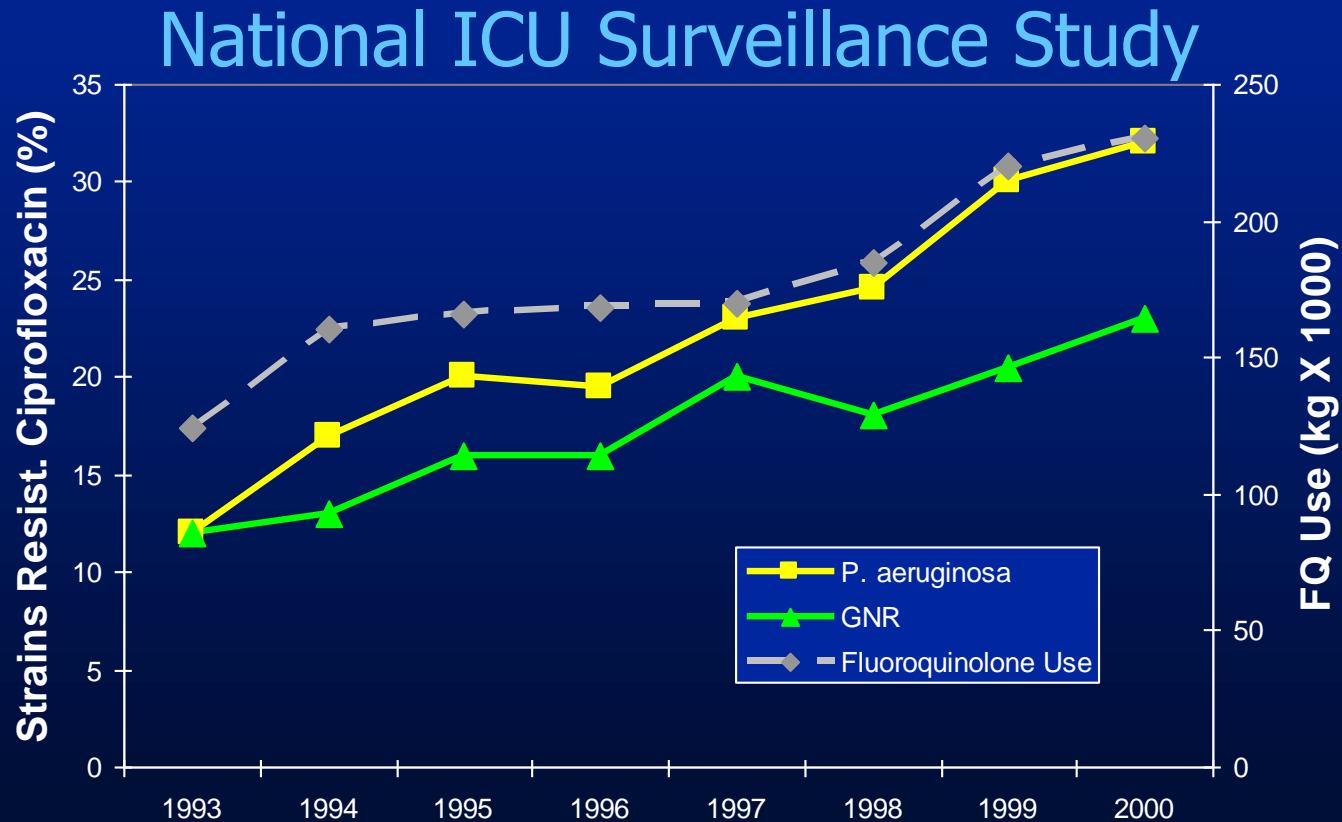


Elixhauser A, et al. Healthcare Cost and Utilization Project: Statistical Brief #50. April 2008. Available at: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf>. Accessed March 10, 2010.

Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.



Fluoroquinolone Use and Resistance among Gram-Negative Isolates, 1993-2000



Neuhauser, et al. *JAMA* 2003; 289:885

Association Between Antibiotic Use and Nonsusceptible Pneumococcal Infection

Study	Infection	% <i>S. pneumoniae</i> who had recent antibiotic use		Odds Ratio	p-value
		Nonsusceptible	Susceptible		
Jackson	Invasive	56%	14%	9.3	0.009
Pallares	Invasive	65%	17%	9.3	<0.001
Tan	Invasive	70%	39%	3.7	0.02
Nava	Invasive	30%	11%	3.5	<0.001
Moreno	Bacteremia	57%	4%	3.6	<0.001
Block	Otitis media	69%	25%	6.7	<0.001

Antibiotic Stewardship

- Definition: A system of informatics, data collection, personnel, and policy/procedures which promotes the optimal selection, dosing, and duration of therapy for antimicrobial agents throughout the course of their use
- Purpose:
 - Limit inappropriate and excessive antibiotic use
 - Improve and optimize therapy and clinical outcomes for the individual infected patient

Ohl CA. *Seminar Infect Control* 2001;1:210-21.

Ohl CA, Luther VP. *J. Hosp. Med.* 2011;6:S4

Dellit TH, et. al. *Clin Infect Dis.* 2007;44:159-177

Antibiotic Stewardship

- Is pertinent to inpatient, outpatient, and long-term care settings
- Is practiced at the
 - Level of the patient
 - Level of a health-care facility or system, or network
- Should be a core function of the medical staff (i.e. doctors and other healthcare providers)
- Utilizes the expertise and experience of clinical pharmacists, microbiologists, infection control practitioners and information technologists

Six Goals of Antibiotic Stewardship Programs

1. Reduce antibiotic consumption and inappropriate use
2. Reduce *Clostridium difficile* infections
3. Improve patient outcomes
4. Increase adherence/utilization of treatment guidelines
5. Reduce adverse drug events
6. Decrease or limit antibiotic resistance
 - Hardest to show
 - Best data for health-care associated gram negative organisms

Stewardship Guidelines

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,¹ Robert C. Owens,² John E. McGowan, Jr.,³ Dale N. Gerding,⁴ Robert A. Weinstein,⁵
John P. Burke,⁶ W. Charles Huskins,⁷ David L. Paterson,⁸ Neil O. Fishman,⁹ Christopher F. Carpenter,¹⁰ P. J. Brennan,⁹
Marianne Billeter,¹¹ and Thomas M. Hooton¹²

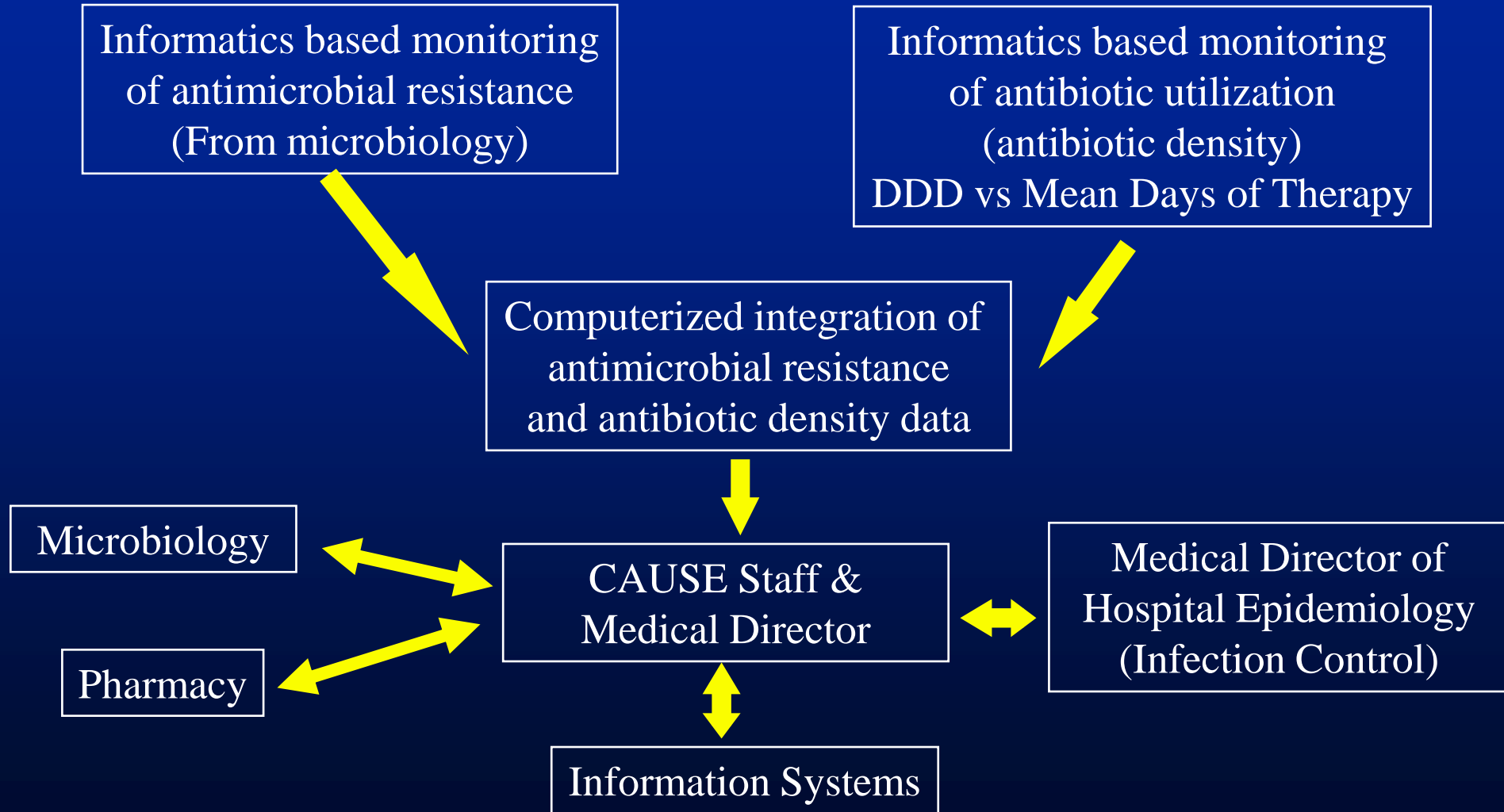
CID 2007;44:159-77

Insights from the Society of Infectious Diseases Pharmacists on Antimicrobial Stewardship Guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Richard H. Drew, Pharm.D., M.S., Roger White, Pharm.D., FCCP, Conan MacDougall, Pharm.D., M.A.S.,
Elizabeth D. Hermsen, Pharm.D., M.B.A., and Robert C. Owens, Jr., Pharm.D.,
on behalf of the Society of Infectious Diseases Pharmacists

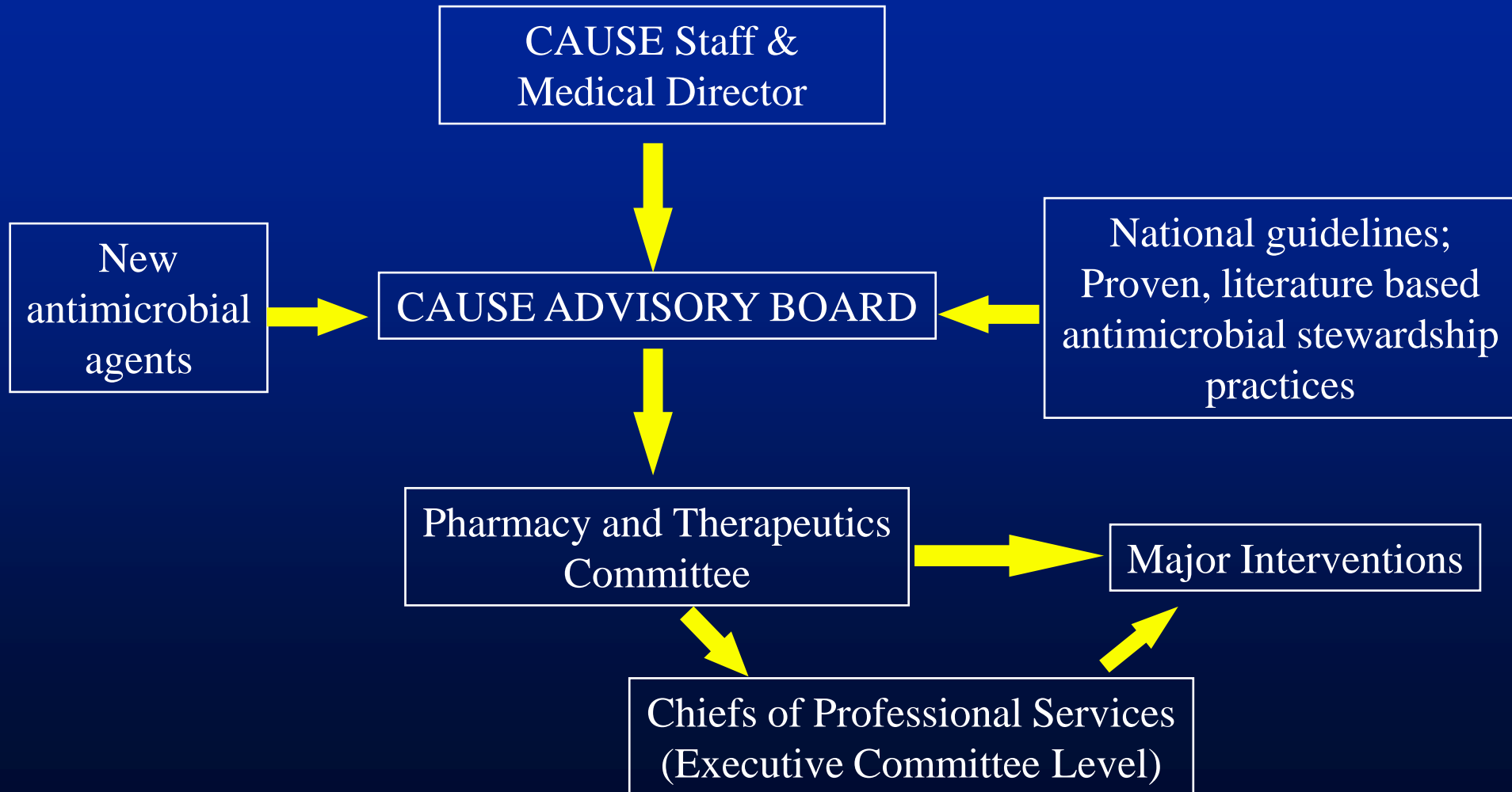
Overview of the Program

Wake Forest Univ. Baptist Medical Center



Overview of the Program

Wake Forest University Baptist Medical Center



Level of the patient



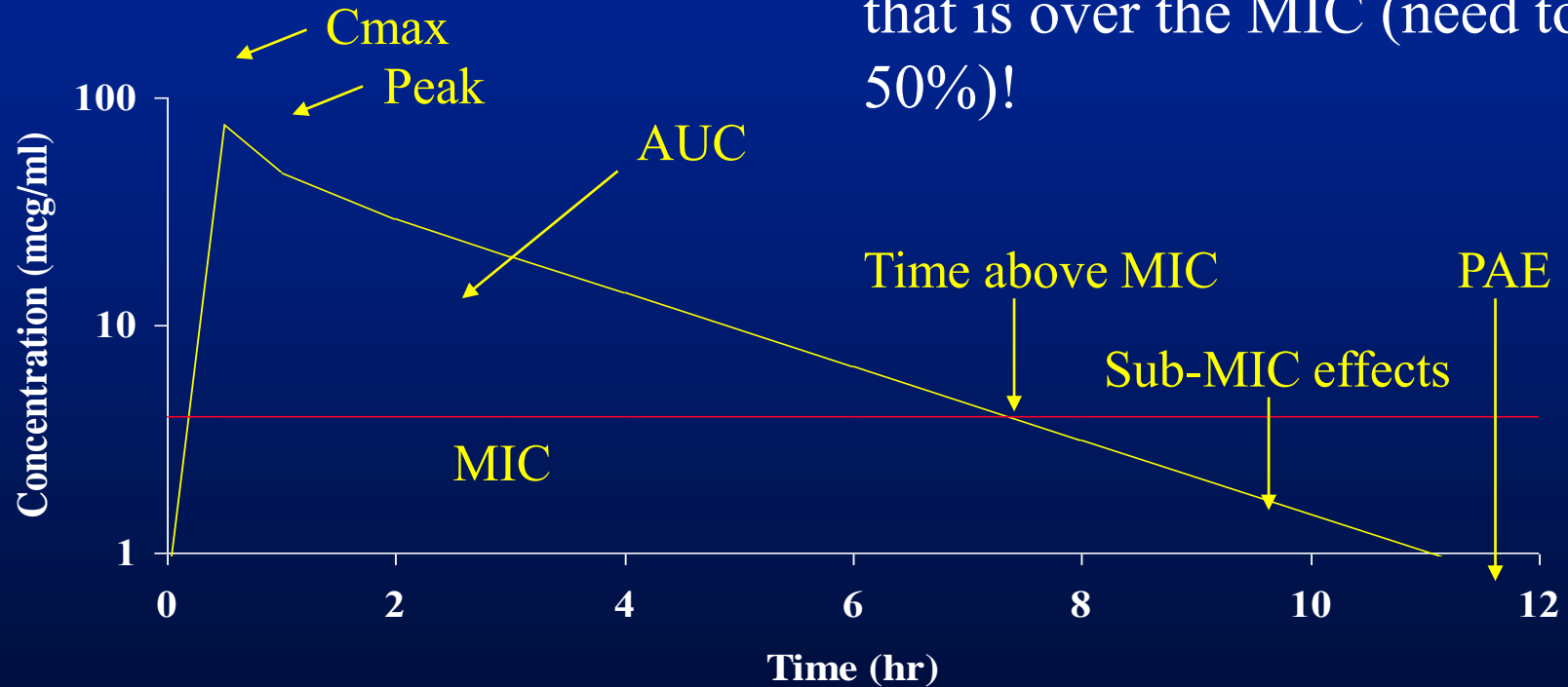
**Level of
the hospital**

IDSA/SHEA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Core elements of a successful antimicrobial stewardship program:

- Prospective audit with intervention and feedback (A-I)
- Formulary restriction and pre-authorization (A-II)

Better dosing and extended infusion: Take advantage of pharmacodynamics



B-lactam antibiotics have time dependent pharmacodynamics

Elements of a successful antimicrobial stewardship program:

Supplemental Interventions

- Guidelines or clinical pathways based on local patterns of use and data



"I'll be happy to give you innovative thinking. What are the guidelines?"

IDSA/SHEA Guidelines for developing an institutional program to enhance antimicrobial stewardship

Elements of a successful antimicrobial stewardship program:

Supplemental Interventions

- Computer Order Entry
 - Informatics support
- Clinical Decision Making



Richards. Med J Aust 2003. 178:36

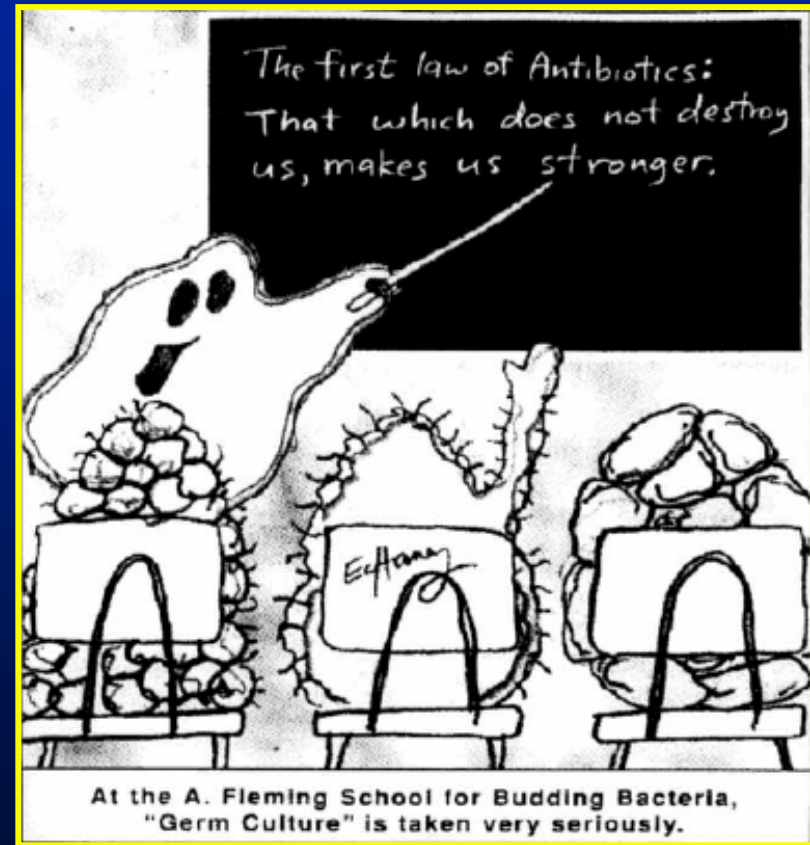
Drew. Am J Health Syst Pharm 2006. 63:957

Pestotnik. Pharmacotherapy 2005 25:1115

Elements of a successful antimicrobial stewardship program:

Supplemental Interventions

- Education
 - Cannot be used alone without other interventions
 - Most useful for “bringing on board” other medical providers and encouraging their participation and cooperation
- Antimicrobial Support Team
- Restricted Antibiotic Pager “consults”
- Need more emphasis in medical school and training programs



IDSA/SHEA Guidelines for developing an institutional program to enhance antimicrobial stewardship

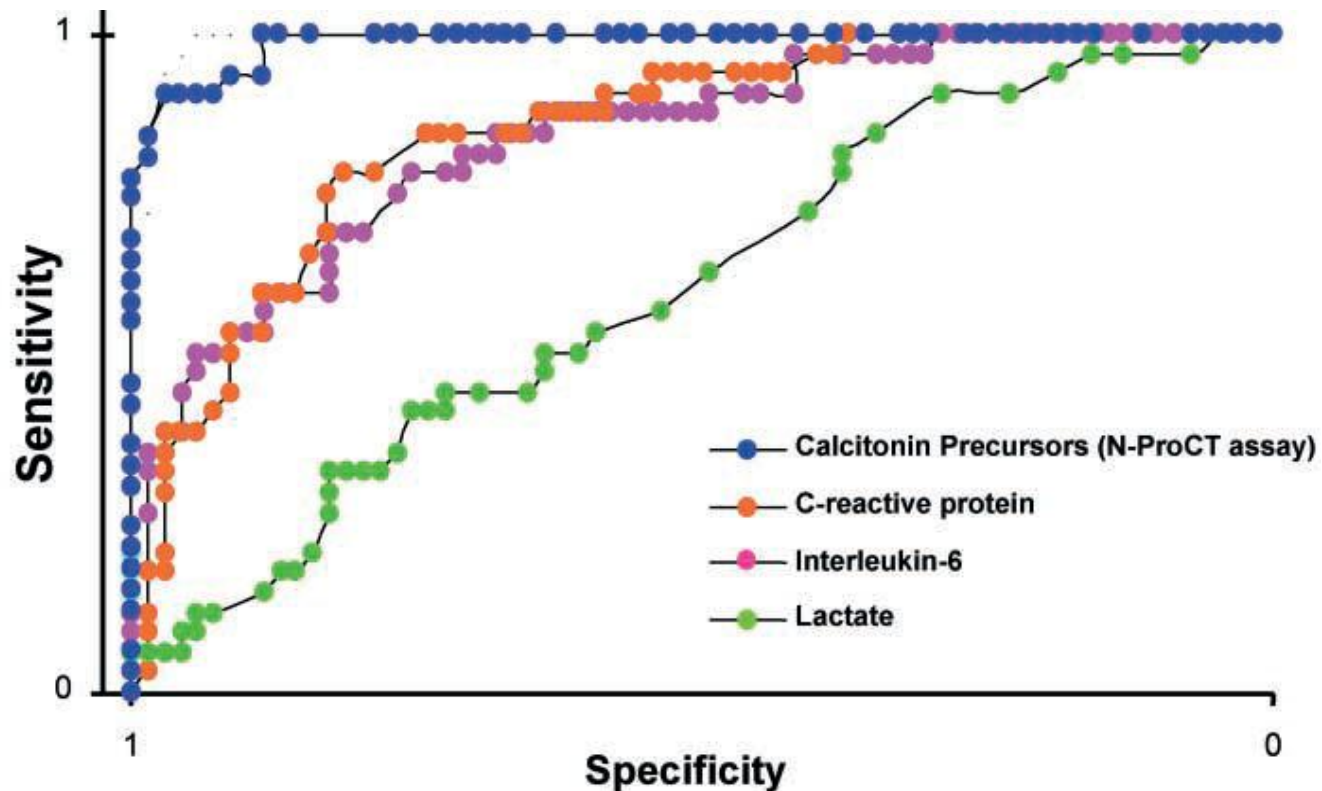
Rapid Molecular Testing: Antimicrobial Stewardship

- Earlier identification of resistant pathogens
 - MRSA from MSSA from CNS
 - *C. albicans* vs nonalbicans candida
 - VRE
- Viral respiratory infections
 - PCR panels now available
- If used need stewardship to intervene and quickly change therapy based on results

Biologic Markers of Sepsis: PCT wins

Diagnostic accuracy of: PCT IL-6 C-reactive protein, lactate in critically ill patients with systemic infections

(i.e. sepsis, severe sepsis, or septic shock) receiver operating curve (ROC) analysis



Improvement in Clinical Outcomes

Impact of Antimicrobial Stewardship

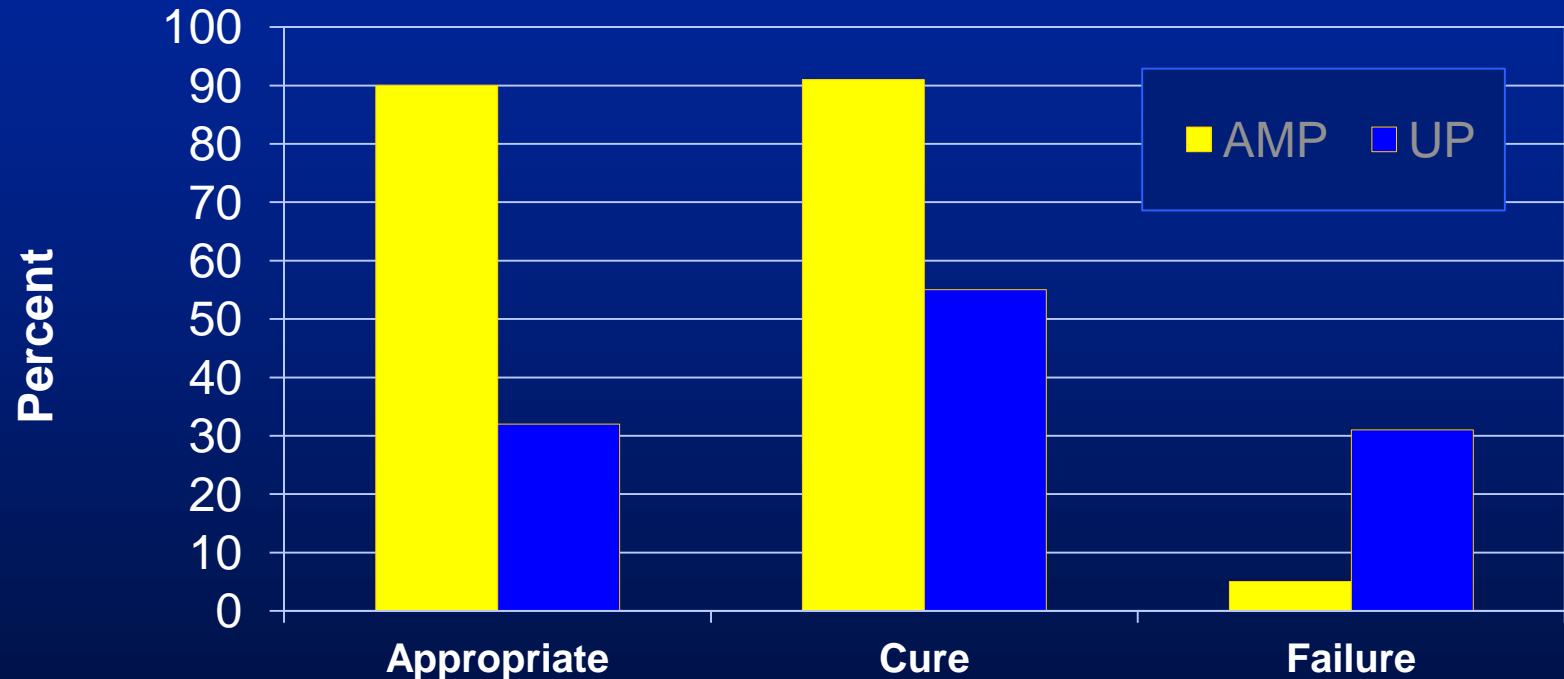
- **Decreased inappropriate use**
 - Fishman N. Am J Med 2006;119:S53
 - Solomon DH, et al. Arch Intern Med. 2001;161:1897-1902
 - Apisarnthanarak A. Clin Infect Dis 2006;42:768
 - Reviewed in Gandhi TN, et al. Crit Care Med. 2010 38:S315-S323
- **Decreased antimicrobial consumption**
 - Frasier GL, et al. Arch Intern Med. 1997 157:1689-94
 - Bantar C, et al. Clin Infect Dis. 2003;37:18
 - Carling P, et al. Infect Control Hosp Epidemiol. 2003;24:699-706
 - Cheng VC, et al. Eur J Clin Microbiol Infect Dis. 2009;28:1447-56.
 - LaRocco A, Jr. Clin Infect Dis. 2003;37:742-3
 - White AC, et al Clin Infect Dis. 1997;25:230-239.
 - Gross R, et al. Clin Infect Dis. 2001 33:289-95

Improvement in Clinical Outcomes

Impact of Antimicrobial Stewardship

- **Adherence with guidelines**
 - Reviewed in Gandhi TN, et al. Crit Care Med. 2010 38:S315-S323
 - Cheng VC, et al. Eur J Clin Microbiol Infect Dis. 2009;28:1447-56.
 - Arnold FW, et al. Infect Control Hosp Epidemiol. 2006;27:378-82.
 - Beardsley J, et al. Chest. 2006 130:787-93
- **Reduced length of hospital stay**
 - White AC, et al Clin Infect Dis. 1997;25:230-239.
 - Frasier GL, et al. Arch Intern Med. 1997 157:1689-94
 - Coleman et. al. Am J Med. 1991;90:439-44
 - Gentry CA, et al. Am J Health Syst Pharm 2000;57:268-74
 - Fishman N. Am J Med 2006;119:S53
- **Improved VAP/ICU outcomes**
 - Reviewed in Gandhi TN, et al. Crit Care Med. 2010 38:S315-S323

Antibiotic Stewardship Improves Clinical Outcomes



RR 2.8 (2.1-3.8)

RR 1.7 (1.3-2.1)

RR 0.2 (0.1-0.4)

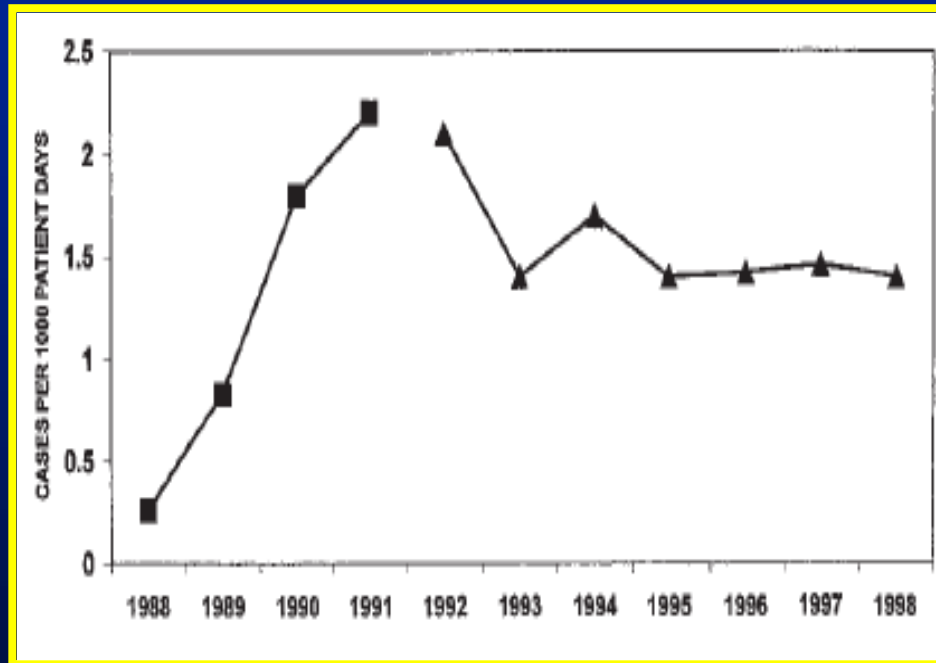
AMP = Antibiotic Management Program

UP = Usual Practice

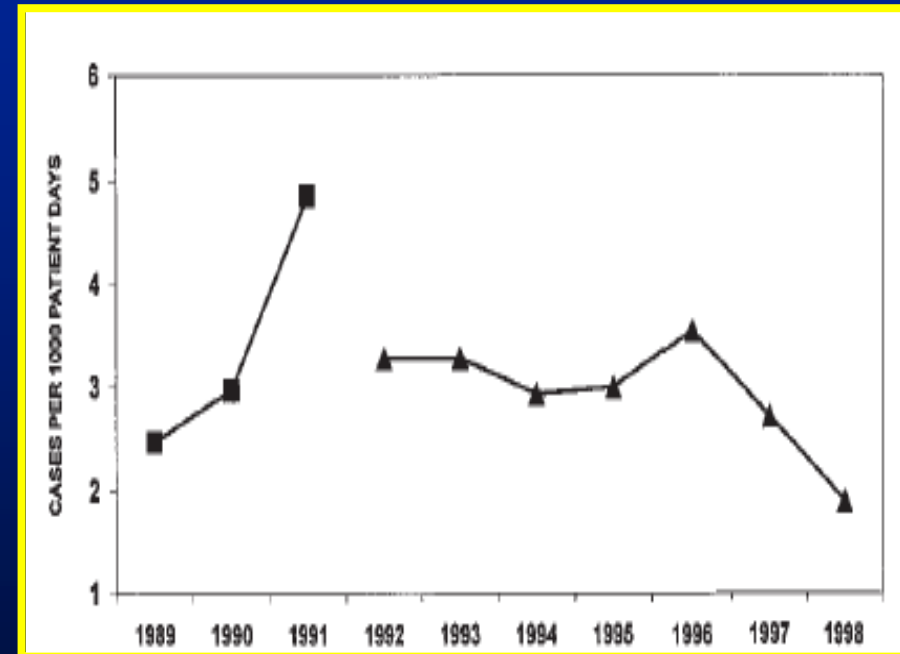
Impact of Prospective Audit and Feedback

Medium-sized Boston Community Teaching Hospital

Rates of *C. difficile* AAD



Rates of Resistant Enterobacteriaceae



Carling P et al. Infect Control Hosp Epidemiol. 2003;24(9):699-706.

CAN ANTIMICROBIAL STEWARDSHIP LIMIT THE EMERGENCE OF RESISTANCE?

Best Evidence for:

- Decreased *C. difficile* AAD
- Decreased resistant Gram-negative bacilli
- Decreased VRE

Carling et al. ICHE 2003;24:699-706

Climo et al. Ann Intern Med 1998;128:989-95

Khan et al. J Hosp Infect 2004;54:104-8

Meyer et al. Ann Intern Med 1993;119:353-8

Pear et al. Ann Intern Med 1994;120:272-7

Bradley et al. J Antimicrob Chemother 1997;40:707-11

de Man et al. Lancet 2000;355:973-8

Singh et al. Am J Respir Crit Care Med 2000;162:505-11

Regal et al. Pharmacotherapy. 2003 23:618-24

Apisarnthanarak A. Clin Infect Dis 2006;42:768

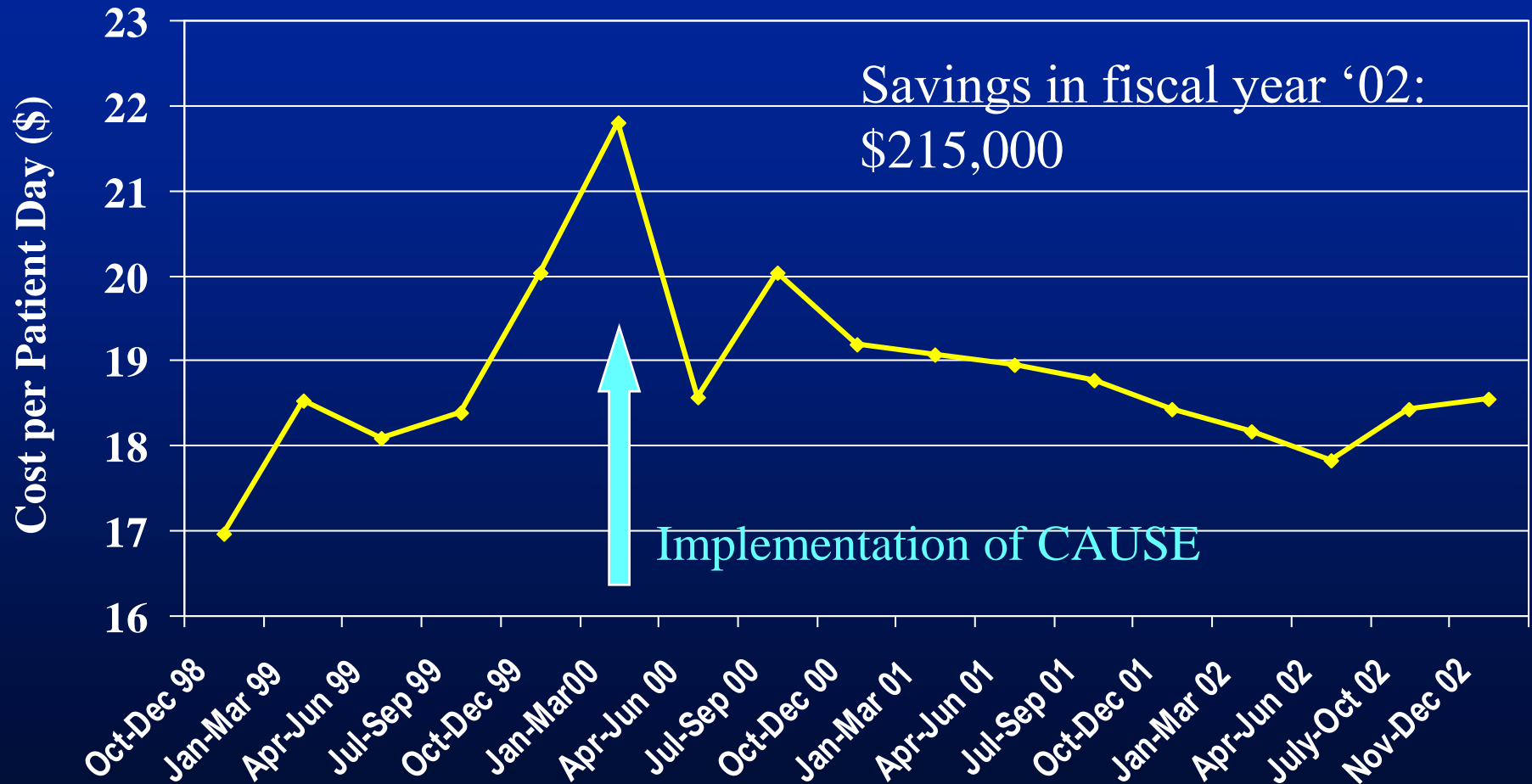
Pakyz et al. Antimicrob Agents Chemother. 2009 53:1983-96

Limitations of Studies Showing Impact of Antimicrobial Stewardship on Resistance

- Selection biases
- Insufficient power
- Varying duration of intervention
- Failure to deal with confounders
 - Cause of resistance is multifactorial
 - Community vs. nosocomial pathogens
 - Many studies done for outbreak control
 - Multiple concurrent control measures
 - Colonization pressure
- Generalizability

Antimicrobial Costs

Before and after Implementation of CAUSE



SHEA/IDSA Policy Statement

- Stewardship initiatives and training should be FUNDED
- Stewardship programs should be REQUIRED through regulatory mechanisms
 - Minimum program: physician and pharmacist trained in antimicrobial stewardship
 - Institutional guidelines
 - Interventions
 - Measurement of antimicrobial use with reporting to NHSN

Potential Quality Measures

- Guiding principles
 - Apply to a wide range of patients
 - Implementable
 - Measurable
- CMS Program
 - Quality Assessment and Performance Improvement (QAPI)
 - Focus is on care delivered to patients, the performance of the hospital as an organization, and the impact of treatment on the health status of the hospital's patients.

Potential Quality Measures

- Requiring an indication with every antibiotic order
 - Pair with #2 below?
 - Would need to specify “allowed” indications
- Antibiotic order is reviewed within 72 hours
 - Pair with #1?
 - Could be done by the treating team and/or ASP
- Cultures are obtained before new antibiotics are administered for sepsis or systemic inflammatory response syndrome
- Required review of all positive blood cultures with appropriate action take if therapy incorrect
 - Bug/drug mismatch
 - Contaminants
- Switch patients who can be switched from IV to oral antibiotics
- Refrain from treating asymptomatic bacteruria

Antibiotic Stewardship Driver Diagram



INSTITUTE FOR
HEALTHCARE
IMPROVEMENT

Timely and appropriate antibiotic utilization in the acute care setting



Decreased incidence of
antibiotic-related adverse drug
events (ADEs)

Decreased prevalence of
antibiotic resistant healthcare-
associated pathogens

Decreased incidence of
healthcare-associated *C. difficile*
infection

Decreased pharmacy cost for
antibiotics

Primary Drivers

Timely and
appropriate initiation
of antibiotics

Appropriate administration
and de-escalation

Data monitoring,
transparency, and
stewardship infrastructure

Availability of expertise at
the point of care

Secondary Drivers

- Promptly identify patients who require antibiotics
- Obtain cultures prior to starting antibiotics
- Do not give antibiotics with overlapping activity or combinations not supported by evidence or guidelines
- Determine and verify antibiotic allergies and tailor therapy accordingly
- Consider local antibiotic susceptibility patterns in selecting therapy
- Start treatment promptly
- Specify expected duration of therapy based on evidence and national and hospital guidelines

- Make antibiotics patient is receiving and start dates visible at point of care
- Give antibiotics at the right dose and interval
- Stop or de-escalate therapy promptly based on the culture and sensitivity results
- Reconcile and adjust antibiotics at all transitions and changes in patient's condition
- Monitor for toxicity reliably and adjust agent and dose promptly

- Monitor, feedback, and make visible data regarding antibiotic utilization, antibiotic resistance, ADEs, *C. difficile*, cost, and adherence to the organization's recommended culturing and prescribing practices

- Develop and make available expertise in antibiotic use
- Ensure expertise is available at the point of care

Leadership and Culture

California Antimicrobial Stewardship Program Initiative

California Senate Bill 739

Mandated that, by January 1, 2008, CDPH require general acute care hospitals to develop a process for the judicious use of antibiotics and monitor antibiotic use by a quality improvement committee

Antibiotic Use Leads to Antibiotic Resistance



Outpatient

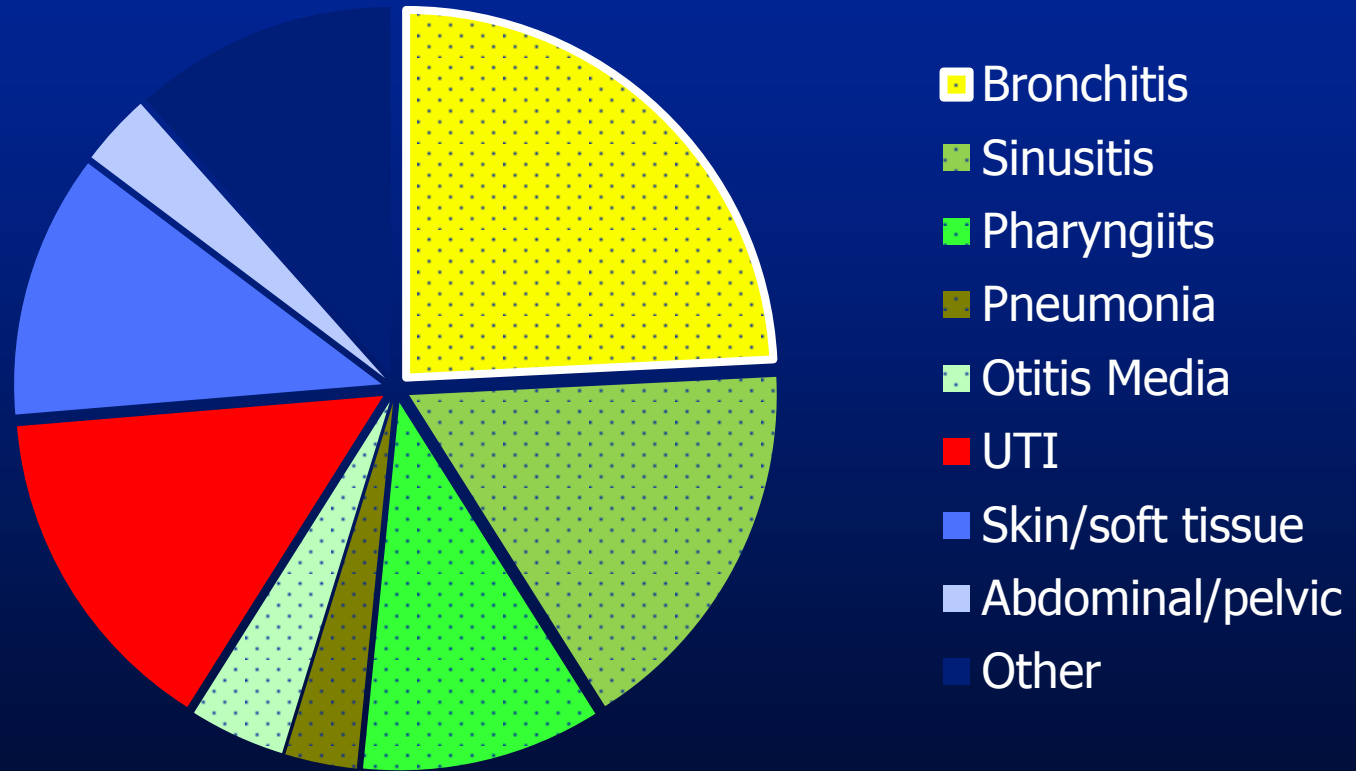
Inpatient



Agriculture

Over half of Antibiotic Use in Adults is for Respiratory Tract Infections

Adult Oral Antibiotic Use by Diagnosis



Reasons for Antibiotic Overuse : Conclusions from 8 Focus Groups

Patient Concerns

- Want clear explanation
- Green nasal discharge
- Need to return to work

Physician Concerns

- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure



Antibiotic Prescription



Snort. Sniffle. Sneeze.

No Antibiotics Please.

**Treat colds and flu with care.
Talk to your doctor.**

As a parent, you want to help your child feel better. But antibiotics aren't always the answer. They don't fight the viruses that cause colds and flu. What will? Fluids and plenty of rest are best. Talk to your doctor. Find out when antibiotics work – and when they don't. The best care is the right care.

**For more information, please call 1-888-246-2675
or visit www.cdc.gov/getsmart.**



OPTIONAL LOCALIZATION:
Your logo can be placed here.

<http://www.cdc.gov/getsmart>



Wisconsin Antibiotic Resistance Network



"Hi, we're the Anti-B's!"

"I'm Annie Biotic!"

"And I'm Moxi Cillin!"

"There's no excuse for overuse!"

**"Click on us to learn why
we're talking about antibiotics!"**

<http://www.wismed.org/warn/home.htm>

Antimicrobial Stewardship

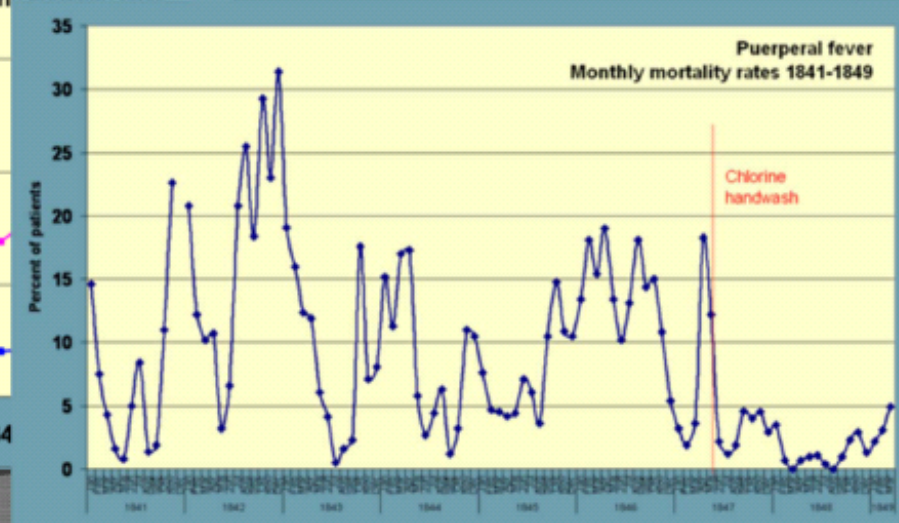
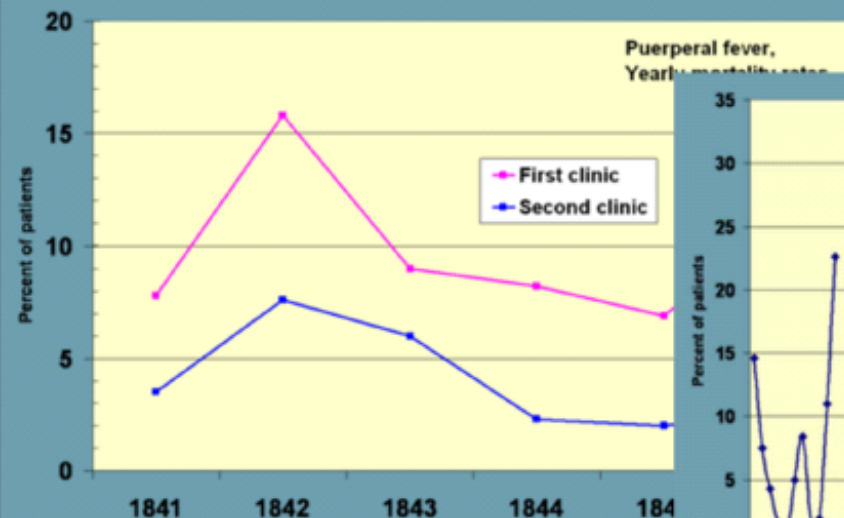
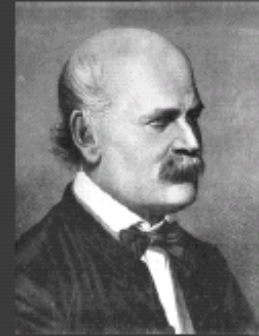
Combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial resistance bacterial



Dellit et. al. Clin Infect Dis 2007;44:159-177

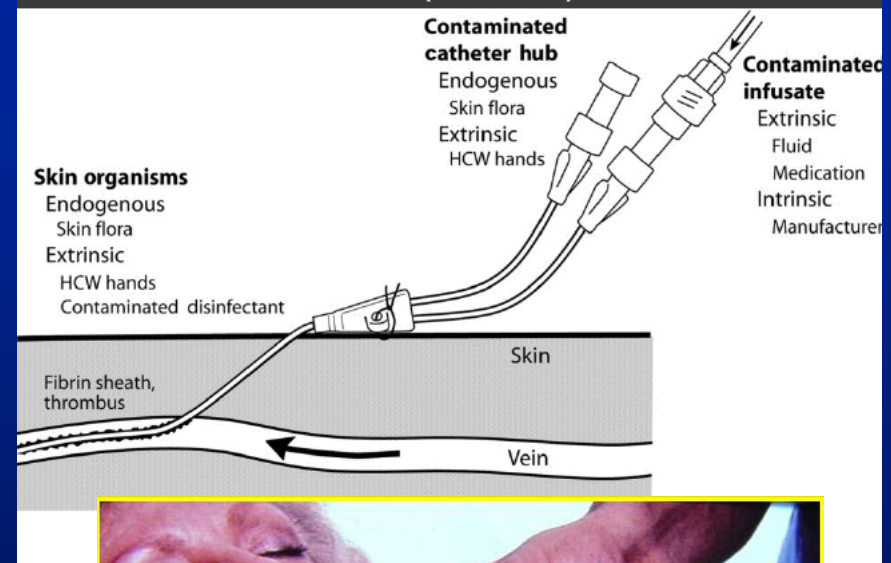
Part I: How it all started...

- Ignaz Semmelweis (1818-1865)
 - HCPs can transmit disease
 - First description of an HAI
 - First Intervention – Hand Hygiene



Fundamentals of Infection Control for MDROs

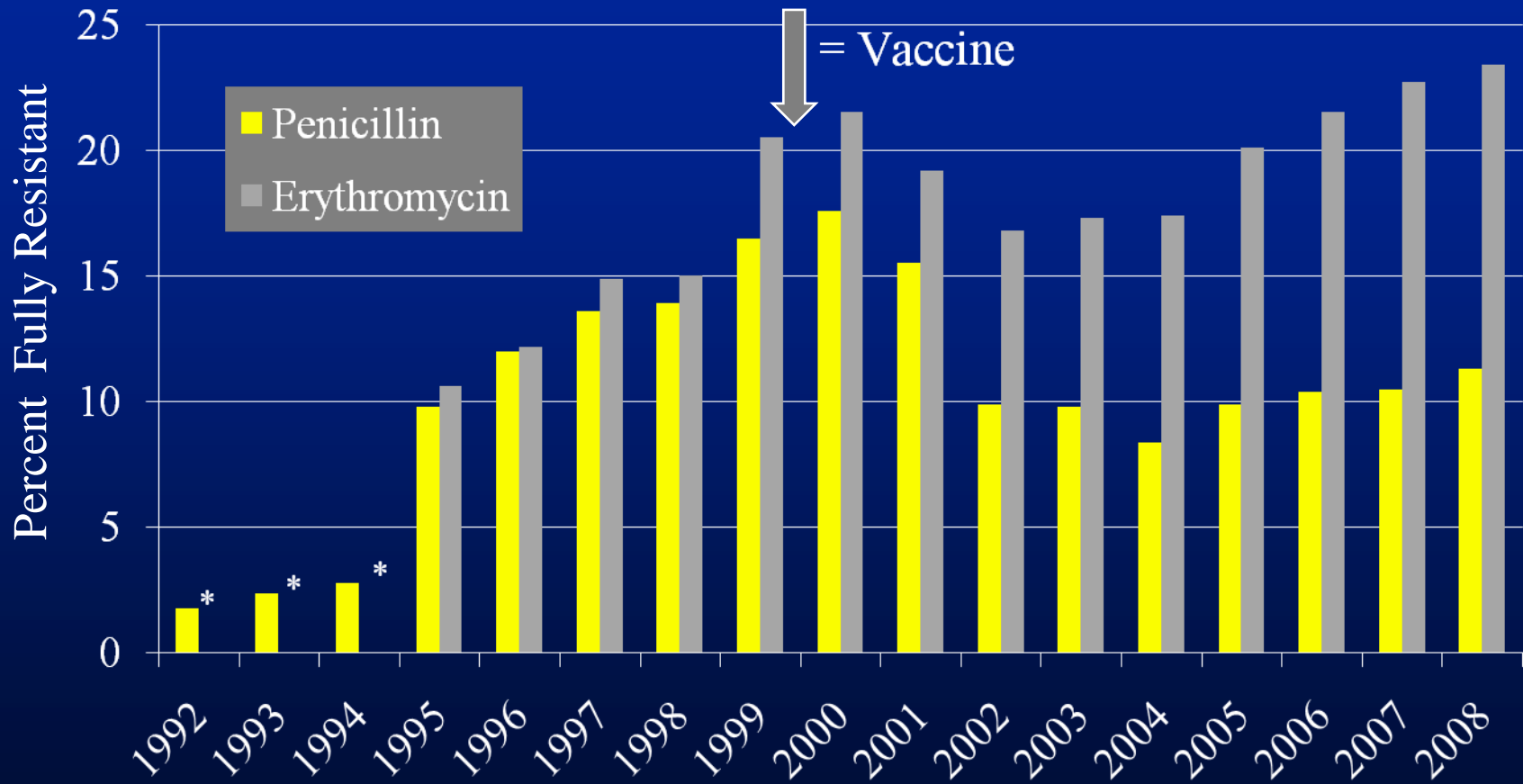
- Hand Hygiene
- Contact Isolation of Patients with Drug Resistant Pathogens
- Gowns and Gloves
- Active Surveillance
- Prevention of Device Related Infections
- Environmental Disinfection





Slowly he
would cruise
the
neighborhood,
waiting for that
occasional
careless child
who confused
him with
another vendor

Proportion of Resistant Invasive *Streptococcus pneumoniae* spp., 1992-2008

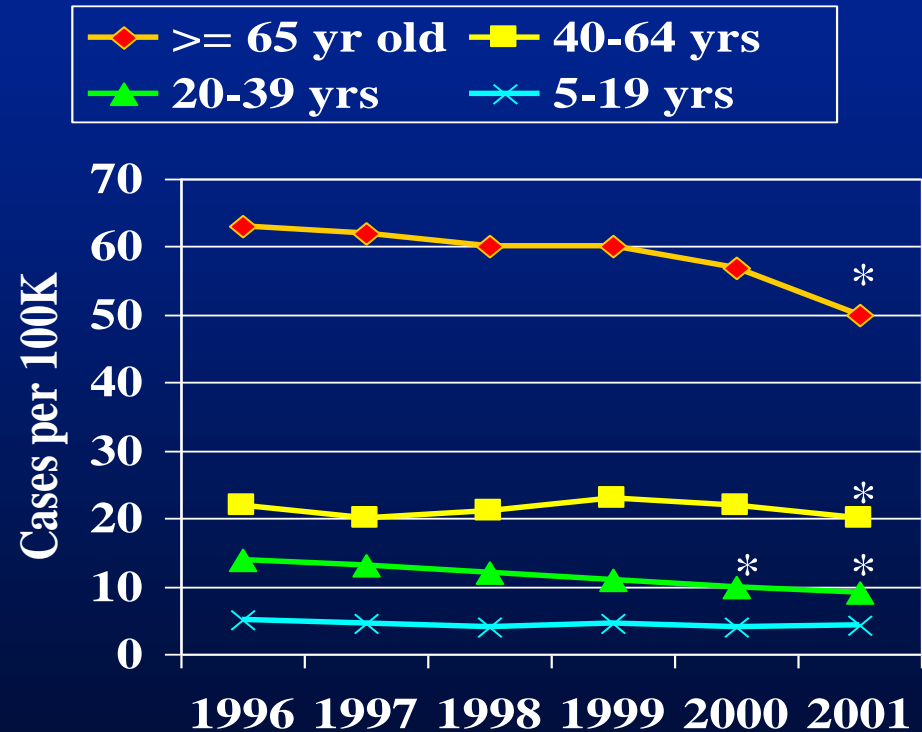


Source: CDC Active Bacterial Core Surveillance and Sentinel Surveillance Network.

•Erythromycin resistance data not available

Impact of Childhood Conjugated Pneumococcal Vaccine on Adult Disease

- Many adults with invasive pneumococcal disease contract the organism from a child
- Rate of change in ≥ 65 yr olds:
 - -22% for 7 vaccine-related serotypes
 - +5% for non-vaccine-related serotypes

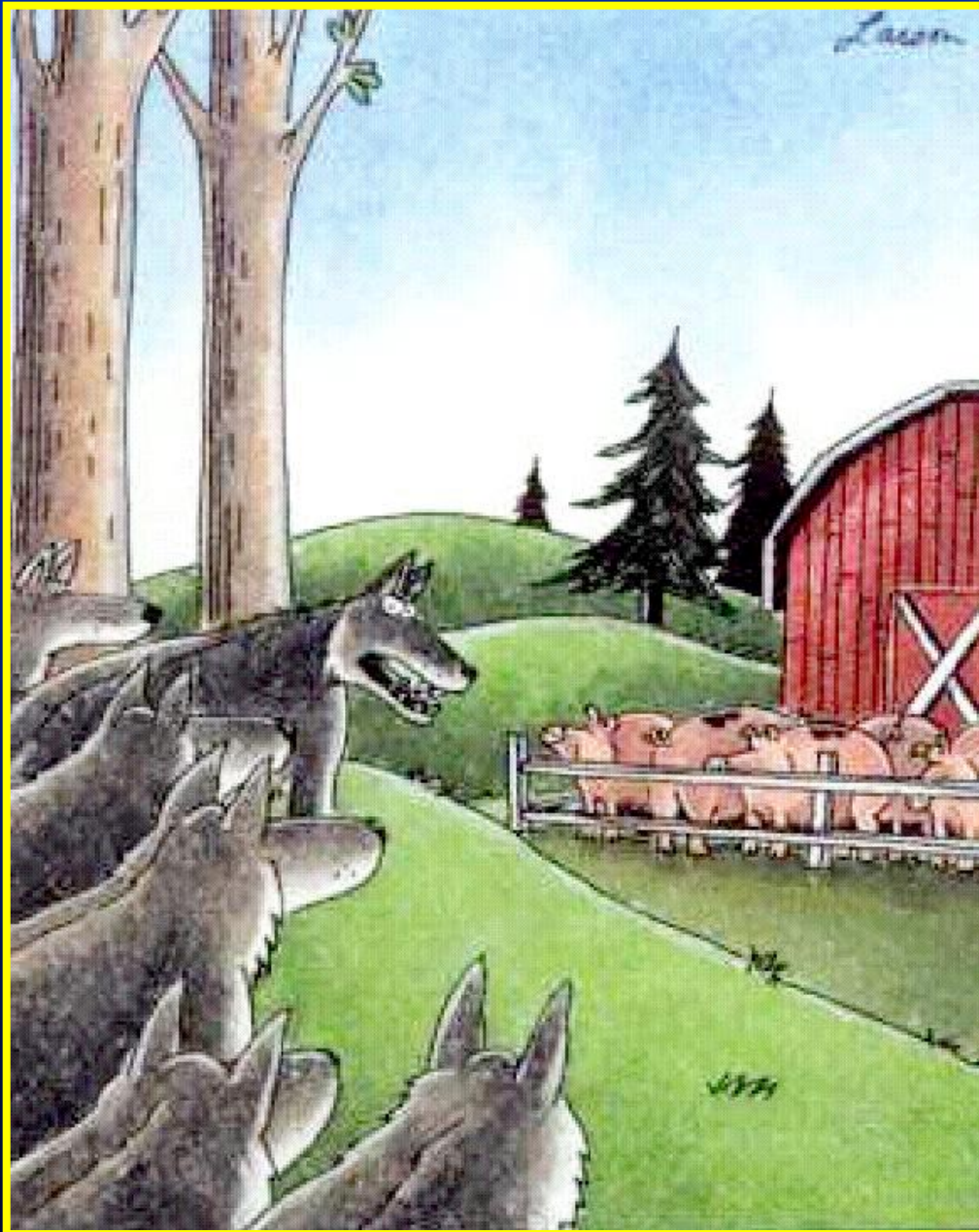


Whitney, et al. NEJM, 2003;348;18:1737-46

Challenges in the Developing World

- MDR TB
- Drug Resistant Malaria
- Counterfeiting
- Over the counter antibiotics
- Poor infection control





“I say we do it ...
and trichinosis
be damned!”